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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/134,333	08/14/1998	SHIRLEY LONGACRE-ANDRE	0660-0135-0X	7863

22850 7590 09/02/2010

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ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
09/02/2010	ELECTRONIC

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/134,333
Filing Date: August 14, 1998
Appellant(s): LONGACRE-ANDRE ET AL.

James J. Kelly, Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11 September 2009 appealing from the Office action mailed 15 December 2008.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

134, 139-142, 145, 148-155, 157, 158, 160, 161, 163, 164, and 166-177.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5,720,959 HOLDER et al. 02-1998

LONGACRE, S., "The *Plasmodium cynomolgi* merozoite surface protein 1 C-terminal sequence and its homologies with other *Plasmodium* species" Molecular and Biochemical Parasitology, Vol. 74 (1995), pp. 105-111.

LONGACRE et al. "*Plasmodium vivax* merozoite surface protein 1 C-terminal recombinant proteins in baculovirus" Molecular and Biochemical Parasitology, Vol. 64 (1994), pp. 191-205.

CHAPPEL et al. "Monoclonal antibodies that inhibit *Plasmodium falciparum* invasion in vitro recognize the first growth factor-like domain of merozoite surface protein-1" Molecular and Biochemical Parasitology, Vol. 60 (1993), pp. 303-311.

MILLER et al. "Analysis of sequence diversity in the *Plasmodium falciparum* merozoite surface protein-1 (MSP-1)" Molecular and Biochemical Parasitology, Vol. 59 (1993), pp. 1-14.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 153, 169, 172, and 175 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Longacre (Mol. Biochem. Parasitol. 74: 105, 1995) in view of Longacre et al. (Mol. Biochem. Parasitol. 64:191, 1994) for reasons of record repeated herein below for convenience.

Longacre teaches the cloning of the *Plasmodium cynomolgi* C-terminal merozoite surface protein (MSP-1) sequence in the $pVLSV_{200}$ plasmid (see Fig. 1 legend), a plasmid containing the N-terminal signal sequence of the MSP-1 protein of *Plasmodium vivax*, containing residues Met_1-Asp_{32} thereof therein, previously shown effective by Longacre et al. (Mol. Biochem. Parasitol. 64:191, 1994; see especially Fig. 2) as a transfer vector for the cloning of the C-terminal p42 and p19 fragments of the *P. vivax* MSP-1 protein in baculovirus. Longacre, in Fig. 1, identifies the p42 and p19 cleavage sites of the *Plasmodium cynomolgi* C-terminal MSP-1 protein sequence. The reference suggests the use of the C-terminal MSP-1 polypeptide fragments for vaccine studies in teaching the substantiated potential of the C-terminal MSP-1 polypeptides as vaccine candidates, in teaching that the C-terminal MSP-1 protein sequence of *Plasmodium cynomolgi* was cloned as a step to vaccine trials with this region of the protein (see e.g. pages 105-107, especially the paragraph bridging pages 106-107) and in specifically teaching the use of a baculovirus for expression of the recombinant *P. cynomolgi* MSP-1 C-terminal protein fragment comprising the conformational epitopes of the epidermal growth factor-like (EGF-like) domains of the p19 fragment (see e.g. paragraph bridging pages 108-109). The reference does not specifically exemplify protein production and isolation, however.

Longacre et al. teach the C-terminal p42 and p19 fragments of MSP-1 proteins as notoriously old and well known vaccine candidates in the art (see e.g., page 192). Longacre et al. teach recombinant baculovirus constructs comprising nucleic acid sequences encoding C-terminal fragments of the *Plasmodium vivax* MSP-1 protein in $pVLSV_{200}$ plasmid-derived transfer vectors, vectors encoding N-terminal signal sequence amino acids of the *Plasmodium vivax* MSP-1 protein, an engineered *Eco*RI restriction site (see page 192 and Fig. 2), either

anchored or secreted forms of both the C-terminal p42 fragment (which comprises the C-terminal p19 fragment) and the C-terminal p19 fragment of the *Plasmodium vivax* MSP-1 protein, and two TAA stop codons all under the control of the polyhedrin promoter, which produce in infected cells either anchored or secreted forms of both the C-terminal p42 fragment (which comprises the C-terminal p19 fragment) and the C-terminal p19 fragment of the *P. vivax* MSP-1 protein (see e.g. pages 192-3, and page 195, Fig. 2). The reference admits that the construction of recombinant baculovirus expressing *P. vivax* MSP-1 protein fragments was guided by the previous functional constructs expressing the *P. falciparum* MSP-1 protein fragments (see e.g. pages 192, 194, 201 and 202). Longacre et al. teach that inclusion of 6 or 7 of the apparently well conserved amino acid residues upstream from the MSP-1 C-terminal cleavage sites in p42 and p19 constructs, as well as the N-terminal signal sequence, are beneficial (see e.g.: page 194, col. 2; or page 201, paragraph bridging cols. 1-2). Longacre et al. (see e.g. page 199) teach that the recombinant p19 polypeptides, more so than the p42 polypeptides, had a tendency to aggregate. The reference teaches that the recombinant polypeptides were produced and isolated for vaccine studies (see e.g. page 202, col. 1, ¶ 1). The reference thus demonstrates that baculovirus constructs containing an appropriate MSP-1 signal sequence can be used for the expression of various length soluble or anchored C-terminal fragments of the MSP-1 protein with tertiary structures resembling the native protein for vaccine studies.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used the plasmid transfer vector and a baculovirus construct containing the encoded cloned *Plasmodium cynomolgi* C-terminal MSP-1 protein sequence, or

similarly constructed plasmids and baculovirus constructs as taught in Longacre et al., in Longacre for the production and isolation of encoded C-terminal MSP-1 protein region or fragments because Longacre desires the *Plasmodium cynomolgi* C-terminal MSP-1 protein region or fragments thereof for vaccine studies and Longacre et al. teach that such similar constructs had been successfully used for protein production and isolation of the homologous fragments from a number of other species of malarial parasites for such studies. One would have had obvious motivation to clone and produce the C-terminal p42 and p19 fragments of MSP-1 proteins because as clearly taught by the references these fragments were notoriously old and well known vaccine candidates in the art. One would have had an extremely reasonable expectation of success in view of the prior success with the homologues from the other species of *Plasmodium* taught in Longacre et al. The identification of the p42 and p19 cleavage sites of the *Plasmodium cynomolgi* C-terminal MSP-1 protein sequence in Fig. 1 of Longacre and the teaching in Longacre et al. to include 6 or 7 of the apparently well conserved amino acid residues upstream from the cleavage sites in p42 and p19 constructs (see e.g. page 194, col. 2, or page 201) would have reasonably guided one of ordinary skill in the art to residues 276-380 of instant SEQ ID NO: 11, and of the sequence in Longacre, for a *P. cynomolgi* MSP-1 p19 construct. The atomic coordinates and fingerprints as claimed are considered a property of the polypeptide which would flow naturally from following the suggestion of the prior art.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 151, 152, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173, and 174 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Chappel et al. (Mol. Biochem. Parasitol. 60:303, 1993), Miller et al. (Mol. Biochem. Parasitol. 59:1, 1993), Longacre et al. (Mol. Biochem. Parasitol. 64:191, 1994), and Longacre (Mol. Biochem. Parasitol. 74: 105, 1995) for reasons of record repeated herein below for convenience.

Chappel et al. teach a recombinant baculovirus, similar in construction to that as instantly disclosed, i.e. having the amino terminal 34 amino acids of the *P. falciparum* merozoite surface protein (MSP-1) fused to 271 amino acid residues of the p42 fragment of the protein ending at residue 1723 of the sequence as disclosed and numbered in Miller et al. (see page 6), which produces a soluble protein (because it lacks the putative glycosylphosphatidylinositol addition region C-terminal to the second epidermal growth factor-like (EGF-like) domain (see e.g.: page 309; or, Longacre et al., page 202)) and which includes both EGF-like domain structures of the p19 fragment of the MSP-1 protein (see e.g. paragraph bridging pages 304-305, and page 305, Fig. 1C). The reference teaches that the first EGF-like domain of the p19 fragment, by itself, contains many of conformational epitopes recognized by known antibodies which bind to both the p42 and p19 fragments and inhibit parasite growth (see e.g. page 303, Abstract, and page 306). The reference teaches that an insect cell product representing correctly folded MSP-1 p42 elicited parasite growth inhibitory antibodies in animals and that even a denatured C-terminal region of the protein had been shown to be partially protective in a primate vaccination model (see e.g. page 309). In contrast to the invention as instantly claimed, the reference does not teach

production of p19 fragments or the use of the N-terminal amino acids of the *Plasmodium vivax* MSP-1 protein.

The teachings of Longacre et al. and Longacre are as set forth previously.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have constructed a recombinant baculovirus expressing at least the first EGF-like domain of the C-terminal p19 fragment of the *P. falciparum* MSP-1 protein using any of the genus of nucleotide sequences encoding the relevant amino acid sequence (Chappel et al. in view of Miller et al.) with well known methods, as in Chappel et al. and Longacre et al., with an extremely reasonable expectation of success that the encoded sequence would be expressed by insect cells containing the baculovirus constructs in view of the successful production of a variety of like soluble and/or anchored MSP-1 fragments as taught in Chappel et al. or Longacre et al. One would have had obvious motivation to clone and produce the C-terminal p42 and p19 fragments of MSP-1 proteins because as clearly taught by the references these fragments were notoriously old and well known vaccine candidates in the art. The identification of at least the p19 cleavage site in Miller et al. (see e.g. pages 6 and 10) and the teaching in Longacre et al. to include 6 or 7 of the apparently well conserved amino acid residues upstream from the cleavage sites in p42 and p19 constructs (see e.g. page 194, col. 2) would have reasonably guided one of ordinary skill in the art to appropriate residues for the *P. falciparum* MSP-1 p19 construct having or not having the well known glycosylphosphatidylinositol addition region C-terminal to the second epidermal growth factor-like (EGF-like) domain. The substitution of *P. vivax* signal and anchoring encoding sequences known to function for expression of the fragments of the MSP-1 protein in insect cells for the homologous sequences encoded by *P. falciparum* is well within the

skill of an ordinary practitioner in the art and would not have been expected to influence the immunological function of the *P. falciparum* encoded and expressed p19 fragment of the MSP-1 protein in view of the teachings of Chappel et al. that the first EGF-like domain of the C-terminal p19 fragment of the *P. falciparum* MSP-1 protein, by itself, contains many of conformational epitopes recognized by known antibodies which bind to both the p42 and p19 fragments and inhibit parasite growth, and one would have had a reasonable expectation of the successful use of a plasmid containing the N-terminal signal sequence of *Plasmodium vivax*, containing residues Met_1-Asp_{32} therein, to function in the cloning of a MSP-1 fragment from a heterologous species in view of its already successful use therefor as taught in Longacre in view of Longacre et al. in a plasmid encoding the C-terminal fragment of the MSP-1 protein of *Plasmodium cynomolgi*. The atomic coordinates and fingerprints as claimed are considered a property of the polypeptide which would flow naturally from following the suggestion of the prior art.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 134, 139-141, 145, 148-150, 176, and 177 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Longacre in view of Longacre et al., as applied to claims 153, 169, 172, and 175 above, and further in view of Holder et al. (US 5,720,959) for reasons of record repeated herein below for convenience.

Claims 134, 139-142, 148, 150, 176, and 177 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chappel et al., Miller et al., Longacre, and Longacre et al., as applied to claims 151, 152, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173, and 174

above, and further in view of Holder et al. (US 5,720,959) for reasons of record repeated herein below for convenience.

The teachings of Longacre in view of Longacre et al., or the combined teachings of Chappel et al., Miller et al., Longacre, and Longacre et al. are as set forth previously and differ from the invention as instantly claimed in not teaching incorporation of recombinant MSP-1 C-terminal polypeptides in vaccine compositions with alum.

Holder et al. teach the merozoite surface protein (MSP-1) of *P. falciparum*, or of other malarial parasite species infectious in humans or mice, as a vaccine candidate (see e.g. col. 1-3) and teach recombinant peptides derived from the 19kDa C-terminal fragment of the MSP-1 of *P. falciparum* which comprise the 2 EGF regions of the p19 protein. The peptides are comprised, in native conformation, in a vaccine administered with an appropriate adjuvant such as alum (see e.g. col. 4).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have incorporated the recombinant MSP-1 C-terminal polypeptides taught by Longacre in view of Longacre et al. or taught by Chappel et al., Miller et al., Longacre, and Longacre et al. in a vaccine composition comprising alum because the recombinant MSP-1 C-terminal polypeptides comprising the EGF-like domains are suggested for use in vaccines and Holder et al. teach the incorporation of MSP-1 polypeptides comprising the EGF domains in vaccine compositions comprising alum.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

(10) Response to Argument

Appellant's arguments filed 11 September 2009, and the declaration of Shirley Longacre, entered 31 July 2006, have been fully considered/reconsidered but they are not deemed to be persuasive.

With regard to rejections over Longacre in view of Longacre et al. together or further in view of Holder et al.

In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

For example, in this regard, appellant urges that Longacre (1995) merely describes the gene sequence of the *P. cynomolgi* MSP-1 p42 for sequence comparisons and does not teach that the amino acid sequence from Lys296 to Ser380 of SEQ ID NO: 11 induces an immune response which can inhibit parasitemia. Appellant further urges that Longacre et al. (1994) do not teach that their constructs can induce an immune response which can inhibit parasitemia.

These arguments are not found persuasive for a number of reasons. Firstly, the argument is unpersuasive because a recitation of intended use or an intended result of the intended use is accorded patentable weight only to the extent that the recitation limits the actual components of a composition; in the instant case the intended use or result thereof does not affect the recombinant protein as claimed in any way which distinguishes over the subject matter taught or suggested by the references as set forth in the rejections of record. Secondly, the argument is also not found

persuasive because the fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. Notwithstanding appellant's assertions to the contrary, as notoriously old and well known in the art as taught in the references and as set forth in the rejections of record, one of ordinary skill in the art would have reasonably expected fragments of various lengths comprising the conformational epitopes of the EGF-like domains of the p19 fragments of plasmodial MSP-1 proteins to function in a vaccine or in the least it would have been obvious to try these fragments because even in the early 1990s, as specifically taught in both Longacre and Longacre et al., the art had "substantiated" the potential of the C-terminal MSP-1 polypeptides as vaccine candidates.

Appellant further urges that neither Longacre nor Longacre et al. teach oligomers of recombinant proteins. This is not found persuasive for the reasons of record in view of the teachings of Longacre et al. regarding the tendency of recombinant p19 MSP-1 fragment molecules to aggregate. The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

In this regard, appellant also urges that Holder et al. do not teach proteins of malarial parasites infectious for man made recombinantly with a baculovirus. This is not found persuasive in view of the combined teachings of Longacre and Longacre et al. The argument is also not found persuasive because the particulars of the polypeptides of Holder et al. are not relied upon in the rejection of record; it is the teaching in the reference to include relevant MSP-1 polypeptide immunogens comprising the EGF domains in vaccine compositions comprising

alum which is relied upon in the rejection of record. Moreover appellant's assertion that Holder et al. teach the sequences of a MSP-1 protein from a murine parasite were not found persuasive because the cited reference (US 5,720,959) teaches *P. falciparum* MSP-1 protein fragments as well as murine fragments and notes the parallel evidence in mouse and man for protective antibodies to the homologous MSP-1 proteins in different species of malarial parasites. It is again noted that, notwithstanding appellant's assertions to the contrary, as notoriously old and well known in the art as taught in the references and as set forth in the rejections of record, one of ordinary skill in the art would have reasonably expected fragments of various lengths comprising the conformational epitopes of the EGF-like domains of the p19 fragments of plasmodial MSP-1 proteins to function in a vaccine or in the least it would have been obvious to try these fragments because even in the early 1990s, as specifically taught in both Longacre and Longacre et al., the art had "substantiated" the potential of the C-terminal MSP-1 polypeptides as vaccine candidates.

Appellant urges that the reference of Arnot et al., comparing responses of various human vaccine candidates produced in insect cells or yeast cells in rabbit trials, provides evidence of unexpected results that should be considered with respect to the obviousness rejection. This is not found persuasive for the reasons of record in view of the teachings in both Longacre and Longacre et al. that the art had "substantiated" the potential of the C-terminal MSP-1 polypeptides as vaccine candidates. Moreover, the argument is unpersuasive in view of Chappel et al. wherein it was shown earlier than the 1993 publication date of the reference, as apparently repeated in Arnot et al., that correctly folded insect cell MSP-1 C-terminal fragment products elicited growth inhibitory antibodies in rabbits better than incorrectly folded but otherwise

identical yeast cell products (see e.g. page 309). The argument is also not found persuasive because the fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. In this regard, the reference of Arnot et al. suggests that the success of the baculovirus product may also be the result of the incorporation of N-terminal block 1 region amino acids in the construct (see e.g. page 1353, col. 2, ¶ 2). The examiner would note that these residues are those included in the N-terminal 34 or 32 amino acid sequence taught in the construct of Chappel et al. and taught as beneficial for use in Longacre et al., respectively. Moreover, the showing in Arnot et al. is not commensurate in scope with the vaccinating composition invention as claimed because the reference did not use alum as the adjuvant.

In response to Appellant's implied arguments that there are no specific suggestions to combine the references, the examiner also recognizes that references cannot be arbitrarily combined and that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See: *In re Nomiya*, 184 USPQ 607 (CCPA 1975); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); or, *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). However, there is no requirement that the claimed invention or a motivation to make the modification be expressly articulated in any one or all of the references. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. See: *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). References are evaluated by

what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 USPQ 545 (CCPA 1969). A person of ordinary skill in the art, using common knowledge and common sense, is capable of fitting the teachings of multiple references together like pieces of a puzzle, regardless of the specific problem being addressed by the individual references. Any need or problem known at the time of the invention can provide a reason for combining elements of the different references. A person of ordinary skill in the art is also a person of ordinary creativity. In this case, for the reasons of record, ample motivations have been set forth to clone and produce the C-terminal p42 and p19 fragments of MSP-1 proteins as notoriously old and well known vaccine candidates in the art as clearly taught by the references (see e.g.: Longacre at al., page 192; Longacre, pages 105-107). Moreover, the examiner would again note the identification of the p42 and p19 cleavage sites in Fig. 1 of Longacre and the teaching in Longacre et al. to include 6 or 7 of the apparently well conserved residues upstream from the cleavage sites in p42 and p19 constructs (see e.g. page 194, col. 2). Such teachings would guide one to residues 276-380 of instant SEQ ID NO: 11, and to the sequence in Longacre, for a *P. cynomolgi* MSP-1 p19 construct. As set forth, Holder et al. teach the incorporation of MSP-1 peptides comprising the EGF domains in vaccine compositions comprising alum.

Notwithstanding appellant's implications to the contrary, the instant use of "comprising" claim language, e.g. in claim 134, does not exclude a longer recombinant protein, as cloned in Longacre, that contains the relevant fragment as instantly claimed. Appellant has provided no description or evidence that inclusion of other residues of the longer sequence materially changes the character of the composition as both the shorter and longer sequences include the EGF-like domains notoriously well known to the art. Indeed, the recombinant protein expressed in

Longacre (1995), with a construct containing the N-terminal signal sequence of *P. vivax*, containing residues Met_1-Asp_{32} therein, with *P. cynomolgi* MSP-1 in view of Longacre et al. (see above and Fig. 1 legend in Longacre (1995) disclosing the use of the $pVLSV_{200}$ plasmid of Longacre et al.), contained relevant conformational epitopes of the p19 fragment (again see page 109).

Appellant urges, in arguments and in the declaration of Shirley Longacre, entered 31 July 2006, that the references as combined do not specifically teach an effective vaccine, particularly one comprising alum. This is not found persuasive for a number of reasons. Firstly, the argument is unpersuasive because a recitation of intended use or an intended result of the intended use is accorded patentable weight only to the extent that the recitation limits the actual components of a composition; in the instant case the intended use or result thereof does not affect the recombinant protein as claimed in any way which distinguishes over the subject matter taught or suggested by the references as set forth in the rejections of record. Secondly, the argument is also not found persuasive because the missing teaching is clearly provided by the combination of the references with the teachings of Holder et al. which provide the direct suggestion to use alum as adjuvant for an MSP-1 fragment vaccine. Thirdly, the argument is also not found persuasive because the fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. Notwithstanding appellant's assertions to the contrary, as notoriously old and well known in the art as taught in the references and as set forth in the rejections of record, one of ordinary skill in the art would have reasonably expected fragments of various lengths comprising the conformational epitopes of the EGF-like domains of the p19

fragments of plasmodial MSP-1 proteins to function in a vaccine or in the least it would have been obvious to try these fragments because even in the early 1990s, as specifically taught in both Longacre and Longacre et al., the art had "substantiated" the potential of the C-terminal MSP-1 polypeptides as vaccine candidates.

With regard to rejections over Chappel et al., Miller et al., Longacre, and Longacre et al. together or further in view of Holder et al.

In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellant's arguments regarding the teachings of Longacre or Longacre et al. or Holder et al. were not found persuasive for the reasons set forth above incorporated herein.

In this regard, appellant urges that Chappel et al. do not teach a construct that has less than the 271 amino acid residues of the S42ΔA construct taught therein. This is not found persuasive in view of the combined teachings of the references as set forth.

Notwithstanding appellant's assertions to the contrary, Chappel et al. is relied upon for the teaching of a recombinant baculovirus producing a soluble *P. falciparum* MSP-1 protein comprising the p19 fragment EGF-like domains, not the fusion proteins as argued.

Moreover, the exercise of pairing the teachings of only some of the cited references, as argued by appellant, is equally unpersuasive. For example, in this regard, appellant urges that the combination of Chappel et al. and Miller et al. only teach cloning of a *P. falciparum* MSP-1

p42 construct having 34, not 32, amino acid residues including the N-terminal signal sequence of the protein. This is not found persuasive in view of the combined teachings of the references as set forth.

In response to Appellant's arguments that there are no specific suggestions to combine the references of Chappel et al., Miller et al., Longacre, and Longacre et al., and further in view of Holder et al., the examiner recognizes that references cannot be arbitrarily combined and that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the common knowledge or common sense generally available to one of ordinary skill in the art. See: *In re Nomiya*, 184 USPQ 607 (CCPA 1975); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); or, *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). However, there is no requirement that the claimed invention or a motivation to make the modification be expressly articulated in any one or all of the references. The test for combining references is what the combination of disclosures, taken as a whole, would suggest to one of ordinary skill in the art. See: *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); or, *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. See: *In re Bozek*, 163 USPQ 545 (CCPA 1969). A person of ordinary skill in the art, using common knowledge and common sense, is capable of fitting the teachings of multiple references together like pieces of a puzzle, regardless of the specific problem being addressed by the individual references. Any need or problem known at the time of the invention can provide a reason for combining elements of the different references. A person of ordinary skill in the art is

also a person of ordinary creativity. In this case, for the reasons of record, ample motivations have been set forth to clone and produce the C-terminal p42 and p19 fragments of MSP-1 proteins comprising the conformational epitopes of the EGF-like domains as notoriously old and well known vaccine candidates in the art as clearly taught by the references (see e.g.: Chappel et al.; Longacre at al., page 192; Holder et al.; Longacre, pages 105-107), or in the least it would have been obvious to try these fragments because of their notoriously old and well known vaccine candidacy. As set forth, one would have had a reasonable expectation of the successful use of a plasmid containing the N-terminal signal sequence of *Plasmodium vivax*, containing residues Met_1-Asp_{32} therein, to function in the cloning of a heterologous species MSP-1 fragment in view of its already successful use therefor as taught in Longacre in view of Longacre et al. As set forth, Holder et al. teach the incorporation of MSP-1 peptides comprising the EGF domains in vaccine compositions comprising alum. Moreover, the examiner would further note the identification of at least the p19 cleavage site in Miller et al. (see e.g. pages 6 and 10) and the teaching in Longacre et al. to include 6 or 7 of the apparently well conserved residues upstream from the cleavage sites in p42 and p19 constructs (see e.g. page 194, col. 2). Such teachings would guide one to appropriate residues for the *P. falciparum* MSP-1 p19 construct. Further, notwithstanding appellant's assertions to the contrary, the instant use of open claim language does not exclude a longer recombinant protein, as cloned in Chappel et al., which comprises the relevant fragment as instantly claimed.

Appellant again urges that the references as combined do not specifically teach an effective vaccine, particularly one comprising alum. This is again not found persuasive for a number of reasons. Firstly, the argument is unpersuasive because a recitation of intended use or

an intended result of the intended use is accorded patentable weight only to the extent that the recitation limits the actual components of a composition; in the instant case the intended use or result thereof does not affect the recombinant protein as claimed in any way which distinguishes over the subject matter taught or suggested by the references as set forth in the rejections of record. Secondly, the argument is also not found persuasive because the missing teaching is clearly provided by the combination of the references with the teachings of Holder et al. which provide the direct suggestion to use alum as adjuvant for an MSP-1 fragment vaccine. Thirdly, the argument is also not found persuasive because the fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. Notwithstanding appellant's assertions to the contrary, as notoriously old and well known in the art as taught in the references and as set forth in the rejections of record, one of ordinary skill in the art would have reasonably expected fragments of various lengths comprising the conformational epitopes of the EGF-like domains of the p19 fragments of plasmodial MSP-1 proteins to function in a vaccine or in the least it would have been obvious to try these fragments because even in the early 1990s, as specifically taught in Longacre, Longacre et al., Holder et al., and/or Chappel et al., the art had substantiated the potential of the C-terminal MSP-1 polypeptides as vaccine candidates.

Appellant arguments regarding evidence of unexpected results in the reference of Arnot et al. have been addressed above and are again not found persuasive for the reasons set forth previously and incorporated herein.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Examiner, Art Unit 1641

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